

Microvascular Dysfunction Is Associated With Worse Cognitive Performance The Maastricht Study

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Microvascular Dysfunction Is Associated With Worse Cognitive Performance The Maastricht Study

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Abstract—Microvascular dysfunction may be associated with worse cognitive performance. Most previous studies did not adjust for important confounders, evaluated only individual measures of microvascular dysfunction, and showed inconsistent results. We evaluated the association between a comprehensive set of measures of microvascular dysfunction and cognitive performance in the population-based Maastricht Study. We used cross-sectional data including 3011 participants (age 59.5 ± 8.2 ; 48.9% women; 26.5% type 2 diabetes mellitus [oversampled by design]). Measures of microvascular dysfunction included magnetic resonance imaging features of cerebral small vessel disease, plasma biomarkers of microvascular dysfunction, albuminuria, flicker light-induced retinal arteriolar and venular dilation response and heat-induced skin hyperemia. These measures were summarized into a microvascular dysfunction composite score. Cognitive domains assessed were memory, processing speed, and executive function. A cognitive function score was calculated as the sum of the scores on these 3 cognitive domains. The microvascular dysfunction score was associated with a worse cognitive function score (standardized β , -0.087 [95% CI, -0.127 to -0.047]), independent of age, education level, sex, type 2 diabetes mellitus, smoking, alcohol use, hypertension, total/HDL (high-density lipoprotein) cholesterol ratio, triglycerides, lipid-modifying medication, prior cardiovascular disease, depression and plasma biomarkers of low-grade inflammation. The fully adjusted β -coefficient of the association between the microvascular dysfunction score and the cognitive function score was equivalent to 2 (range, 1–3) years of aging for each SD higher microvascular dysfunction score. The microvascular dysfunction score was associated with worse memory and processing speed but not with worse executive function. The present study shows that microvascular dysfunction is associated with worse cognitive performance. (*Hypertension*. 2020;75:237–245. DOI: 10.1161/HYPERTENSIONAHA.119.13023.) • [Online Data Supplement](#)

Key Words: blood pressure ■ cerebral small vessel disease ■ cognition ■ dilation ■ hyperemia
■ hypertension ■ microcirculation

Cognitive impairment and dementia are major health problems, and their prevalence rises with the aging of the population.¹ The mechanisms underlying cognitive impairment remain, however, incompletely understood, and may include microvascular dysfunction and damage (MVD).²

The microvasculature is involved in the regulation of many cerebral processes, notably neurovascular coupling, cerebral autoregulation, blood-brain barrier permeability, and neurogenesis.² Impairment of these processes may lead to neuronal

dysfunction, ischemia and cell death, which may contribute to cognitive impairment.²

Microvascular function can be measured noninvasively in various organs. Indirect measures include magnetic resonance imaging (MRI) features of cerebral small vessel disease (CSVD, eg, total brain parenchyma volume, white matter hyperintensity volume, and presence of lacunar infarcts and cerebral microbleeds)³; plasma biomarkers of MVD (eg, sICAM-1 [soluble intercellular adhesion molecule-1], sVCAM-1 [soluble vascular adhesion molecule-1], sE-selectin [soluble E-selectin],

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and vWF [von Willebrand factor]]⁴; and albuminuria (urinary albumin excretion [UAE]).⁵ In addition, direct measures include flicker light-induced retinal arteriolar and venular dilation response⁶ and heat-induced skin hyperemia.⁶ CSVD features are closely linked to brain microvasculature structure, and evidence indicates that these features originate from cerebral MVD.^{3,7,8}; retinal arteriolar and venular dilation response are also closely linked to the brain microvasculature⁹; in addition, to the extent that MVD is a generalized phenomenon, plasma biomarkers of MVD, UAE, and skin hyperemia may also reflect brain MVD.¹⁰

These various measures of MVD (ie, features of CSVD, plasma biomarkers of MVD, UAE, retinal arteriolar and venular dilation response, and skin hyperemia) may, therefore, be summarized into a total MVD composite score. A composite score reduces the influence of the biological variability of its components, as we assume substantial overlap among mechanisms underlying the associations between the MVD measures and cognitive performance. Furthermore, it reduces the chance of a type 1 error. However, no study evaluated the association between such a MVD composite score and cognitive performance.

Some individual MVD measures, that is, CSVD features, plasma biomarkers of MVD and UAE, have been associated with worse cognitive performance,^{11–19} although not all measures consistently so.^{15,20,21} In the Maastricht Study, we previously found a cross-sectional association between higher UAE and worse cognitive performance.²² Previous studies, but not all, were relatively small ($n < 200$),^{11,20} used selected populations,^{11,20,21} and may have been affected by residual confounding due to incomplete adjustment for education level and cardiovascular risk factors.^{11,12,14} Furthermore, most studies did not adjust for depression or low-grade inflammation, although both factors are linked to MVD and worse cognitive performance.^{14,23,24} Moreover, the associations between retinal arteriolar and venular dilation response and skin hyperemia, and cognitive performance have not been investigated.

We, therefore, investigated in a large population-based cohort with participants aged 40 to 75 years, whether a composite score of MVD measures, including CSVD features, plasma biomarkers of MVD, UAE, retinal arteriolar and venular dilation response and skin hyperemia, is associated with worse cognitive performance. We additionally evaluated whether any such association was independent of age, education level, sex, lifestyle factors, cardiovascular risk factors, current depression, and low-grade inflammation.

Methods

Study Population

We used data from The Maastricht Study, an observational population-based cohort study. The rationale and methodology have been described previously.²⁵ In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of diabetes mellitus type 2 (T2D) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged 40 to 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, the municipal registries, and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2D status, with an oversampling of individuals with T2D, for reasons of efficiency. The present study includes cross-sectional data from 3451 participants who completed the baseline survey between November 2010 and September 2013. The examinations of each

participant were performed within a time window of three months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Ministry of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent. Data are available from The Maastricht Study for any researcher who meets the criteria for access to confidential data, and the corresponding author may be contacted to request data.

Microvascular Dysfunction

For all MVD measures, participants were asked to refrain from smoking and drinking caffeine-containing beverages 3 hours before the measurement. A light meal was allowed until ≥ 90 minutes before the examination. For retinal measurements, pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine at least 15 minutes before the start of the examination. Skin blood flow measurements were performed in a climate-controlled room at 24°C.

Cerebral Small Vessel Disease

Brain MRI measurements were implemented from December 2013 onwards and were available in 2313 of 3451 participants (67%). Brain MRI was performed on a 3T MRI scanner (Siemens Magnetom Prisma-fit Syngo MR D13D Erlangen, Germany). We evaluated 4 CSVD features, that is, total brain parenchyma volume, white matter hyperintensity volume, and presence of lacunar infarcts and cerebral microbleeds.³ A detailed description of the MRI protocol and the definitions of the CSVD features is provided in Item S1 in the [online-only Data Supplement](#). The MRI protocol consisted of a 3D T₁-weighted sequence, a fluid-attenuated inversion recovery sequence, a combined proton density and T₂-weighted turbo spin-echo sequence and a susceptibility-weighted imaging sequence.²⁶ Volumes were determined semi-automatically, and lacunar infarcts and cerebral microbleeds were scored manually.

Plasma Biomarkers of MVD

We measured 4 plasma biomarkers of MVD: sICAM-1, sVCAM-1, sE-selectin, and vWF.⁴ sICAM-1, sVCAM-1, and sE-selectin were measured in EDTA plasma samples with commercially available 4-plex sandwich immunoassay kits with different standards and antibodies (Meso Scale Discovery, Rockville, Maryland). For this technique in this study, the intra- and inter-assay coefficients of variation were 10.3 and 8.4% for sICAM-1, 5.0 and 4.7% for sVCAM-1, and 2.9 and 7.4% for sE-selectin, respectively. vWF was quantified in citrate plasma using ELISA (Dako, Glostrup, Denmark). The intra- and inter-assay coefficients of variation were 3.0 and 4.3%, respectively.

Urinary Albumin Excretion

We assessed UAE in two 24-hour urine samples. Urinary albumin concentration was measured with a standard immunoturbidimetric assay by an automatic analyzer (due to a change of supplier, by the Beckman Synchron LX20 and the Roche Cobas 6000) and multiplied by collection volume to obtain 24-hour UAE.²² A urinary albumin concentration below the detection limit of the assay was set at 1.5 mg/L (2 mg/L for the Beckman Synchron LX20 and 3 mg/L for the Roche Cobas 6000) before multiplying by collection volume. Only urine collections with a collection time between 20 and 28 hours were considered valid. If needed, UAE was extrapolated to 24-hour excretion. For this study, UAE was preferably based on the average of 2 (available in 91.3% of participants) 24-hour urine collections.

Flicker Light-Induced Retinal Arteriolar and Venular Dilation Response

We measured retinal arteriolar and venular dilation response to flicker light exposure by the Dynamic Vessel Analyzer (Imedos, Jena, Germany), as previously described.^{6,27} A baseline recording of 50 seconds was followed by 40-second flicker light exposure followed by a 60-second recovery period. We calculated baseline diameters (in measurement units) as the average diameter during 20 to 50 seconds recording. For both the arteriolar and venular dilation response,

percentage dilation over baseline was calculated using the average dilation achieved at time points 10 and 40 seconds during the flicker stimulation period.

Heat-Induced Skin Hyperemia

We measured heat-induced skin hyperemia by laser Doppler flowmetry (Perimed, Järfälla, Sweden), as previously described.⁶ We recorded unheated skin blood flow at the wrist, expressed in arbitrary perfusion units, for 2 minutes to serve as a baseline. After 2 minutes, the temperature of the laser Doppler probe was rapidly and locally increased to 44°C and was kept constant until the end of the registration. Skin hyperemia was expressed as the percentage increase in average perfusion units during the 23 minutes heating phase over the 2 minutes average baseline perfusion units.

Cognitive Performance

We assessed cognitive performance by a concise neuropsychological test battery.²⁵ For statistical efficiency, we constructed a cognitive function score by summation of standardized test scores of 3 cognitive domains: memory, information processing speed, and executive function. A detailed description of methods used to calculate domain-specific cognitive scores is provided in Item S2. We evaluated memory with the Verbal Learning Test.²⁸ Information processing speed was evaluated with the Stroop Color-Word Test Part I and II,²⁹ Concept Shifting Test Part A and B,³⁰ and Letter-Digit Substitution Test.³¹ Executive function was evaluated with the Stroop Color-Word Test Part III and Concept Shifting Test Part C.

Covariates

We determined diabetes mellitus status according to the World Health Organization 2006 criteria as normal glucose metabolism, prediabetes mellitus, or T2D.²⁵ Education level was classified into 3 groups: low (none, primary or lower vocational education only), intermediate (intermediate general secondary, intermediate vocational or higher general secondary education), and high (higher vocational education or university level of education). Alcohol consumption (none, low, high), smoking status (never, former, current), prior cardiovascular disease (CVD), medication use, body mass index, office and ambulatory blood pressure, plasma lipid levels were determined as described previously.^{5,6,25} Hypertension was defined as an office blood pressure $\geq 140/90$ mmHg or use of antihypertensive medication. The Mini-International Neuropsychiatric Interview was used to assess the presence of a current DSM-IV defined minor or major depressive episode, as described previously.²⁵ Plasma biomarkers of low-grade inflammation were determined as described previously.³² These included high-sensitive CRP (C-reactive protein), SAA (serum amyloid A), IL-6 (interleukin-6), IL-8 (interleukin-8), and TNF- α (tumor necrosis factor- α).

Statistical Analysis

We selected all participants who had data available on all potential confounders, at least one individual MVD measure, and cognitive function. We did not impute missing values. We inversed total brain parenchyma volume, retinal arteriolar and venular dilation response and skin hyperemia so higher values indicated MVD. White matter hyperintensity volume was log-transformed (base 2) to normalize its skewed distribution. We analyzed UAE as a categorically (<15 [reference], $15\text{--}30$, and ≥ 30 mg/24 h), because UAE and cognitive performance were nonlinearly associated.

We calculated a MVD composite score (MVD score) of all individual MVD measures. For the total MVD score, the individual 12 MVD measures (ie, 4 CSVD features, 4 plasma biomarkers of MVD, UAE, retinal arteriolar, and venular dilation responses and skin hyperemia) were standardized into z-scores. These z-scores were averaged, and this average was standardized into the MVD score. The MVD score was calculated only in participants with data available on at least 9 of the 12 individual MVD measures. The Cronbach's alpha for measuring internal consistency³³ among the individual MVD measures was 0.52. This is considered acceptable internal consistency

for different measures that may reflect, at least in part, the same underlying construct.³⁴

We used linear regression to investigate the association between the MVD score and the cognitive function score. All analyses were adjusted for age, education level, sex, T2D, body mass index, smoking, alcohol use, hypertension, total/HDL cholesterol ratio, triglycerides and lipid-modifying medication (model 1), and additionally for prior CVD, current depression and the plasma biomarkers of low-grade inflammation, that is, CRP, SAA, IL-6, IL-8, and TNF- α (model 2). Prior CVD, current depression and low-grade inflammation were entered into a separate model, because of the risk of over adjustment bias: these factors may be confounders but may also mediate the association between MVD and cognitive performance.

We tested interaction terms with age (dichotomized into <65 and ≥ 65 years), education level, sex and T2D to evaluate whether the association between MVD and cognitive performance differed according to these factors. Interaction with age and education level was tested because MVD may be more strongly associated with worse cognitive performance in individuals with lower cognitive reserve, that is, in those with higher age and lower education level.³⁵

Several sensitivity analyses were performed. First, we repeated the analysis using domain-specific cognitive function scores as the outcome, that is, memory, processing speed and executive function. Second, we repeated the analysis using each individual MVD measure as the determinant. Third, we repeated the analysis with the MVD score in participants with data available on at least one, eight and 10 of the 12 individual MVD measures, respectively. Fourth, to test whether the association between the MVD score and cognitive function score was primarily determined by individual MVD measures, we repeated the analysis 5 \times after consecutively excluding from the MVD score the CSVD features, plasma biomarkers of MVD, UAE, retinal arteriolar and venular dilation response and skin hyperemia, respectively. Fifth, we calculated composite scores for the CSVD features, plasma biomarkers of MVD and retinal arteriolar and venular dilation response, respectively, and evaluated the association between these composite scores and cognitive function score. The CSVD composite score was calculated as described previously.³⁶ One point per CSVD feature was assigned for: fourth quartile lower total brain parenchyma volume and higher white matter hyperintensity volume; and presence of lacunar infarcts and cerebral microbleeds. The points for each feature were combined into the CSVD score (range, 0–4). For the plasma biomarkers of MVD score and retinal arteriolar and venular dilation response scores, the z-scores of the 4 plasma biomarkers of MVD and the arteriolar and venular dilation responses were summed and standardized, respectively. Sixth, we repeated the analysis with additional adjustment for average 24-hour ambulatory systolic blood pressure,³⁷ and class of antihypertensive medication (ie, angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers versus other classes).^{38,39} Ambulatory systolic blood pressure is a better predictor of cognitive decline than office blood pressure.⁴⁰ However, we did not adjust for ambulatory systolic blood pressure in the main analysis, because data on ambulatory systolic blood pressure were missing in a relatively large number of participants ($n=24$). Seventh, we repeated the analysis after stratification by T2D status, because by design individuals with T2D were oversampled in our cohort.

All analyses were performed with SPSS software (v22.0; IBM, Chicago). A P value of <0.05 , and a P value for interaction of <0.10 for interaction with sex and T2D were considered statistically significant. For interaction with age and education level, a Bonferroni-corrected P value of <0.05 was used instead of <0.10 , because higher age and lower education level are considered reflections of the same construct, that is, lower cognitive reserve.

Results

Figure 1 shows the derivation of the final study population. In total, 3011 participants had data available on all potential confounders and at least one individual MVD measure. The MVD score was available in 2034 participants, CSVD features in 2002, plasma biomarkers of MVD in 2991, UAE in 2987, retinal arteriolar and venular dilation response in

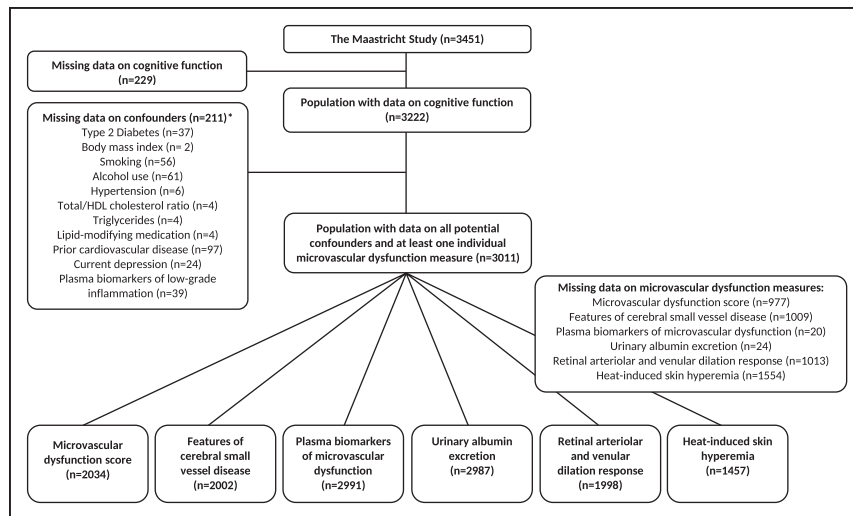


Figure 1. Derivation of the final study populations. *Missings were not mutually exclusive.

1998, and skin hyperemia in 1457. These populations were comparable with regard to age, sex, and cardiovascular risk profile (Table S1). The table shows the characteristics of the study population and according to tertiles of the cognitive function score. Population-characteristics according to tertiles of memory, processing speed, and executive function are provided in Tables S2 through S4. The study population had a mean age of 59.5 years, 48.9% were women, 26.5% had T2D (oversampled by design), and 41.1% had a high education level.

The MVD score was statistically significantly associated with a worse cognitive function score (Figure 2, models 1 and 2). The regression coefficients of all covariates included in the fully adjusted model are provided in the Table S5. The fully adjusted β -coefficient of the association between one SD higher MVD score and the cognitive function score was equivalent to 2 (range, 1–3) years of aging.

Statistically, significant interaction was found between the MVD score and age (P value for interaction 0.045), indicating that the association between MVD and worse cognitive function was stronger in participants aged ≥ 65 as compared with those aged < 65 years. The association between the MVD score and cognitive function score stratified by age is provided in Table S6. We found no interactions with education level, sex, and T2D.

Sensitivity Analyses

The MVD score was statistically significantly associated with worse memory and processing speed, but not with executive function (Figure 3). The individual MVD measures lower total brain parenchyma volume, higher white matter hyperintensity volume, sE-selectin, and UAE > 30 versus < 15 mg/24 h were statistically significantly associated with a worse cognitive function score, but not lacunar infarcts, microbleeds, sICAM-1, sVCAM-1, vWF, UAE 15 to < 30 versus < 15 mg/24 h, retinal arteriolar, and venular dilation responses or skin hyperemia (Figure 4 and Table S7). Results were similar when we repeated the analyses in participants with data available on at least one ($n=3011$), 8 ($n=2364$), or 10 ($n=1658$) of the 12 individual MVD measures (Table S8), and when we consecutively excluded, from

the MVD score, the CSVD features, plasma biomarkers of MVD, UAE, retinal arteriolar and venular dilation response or skin hyperemia (Table S9). The composite scores of CSVD features and plasma biomarkers of MVD, but not of retinal arteriolar and venular dilation responses, were statistically significantly associated with a worse cognitive function score (Table S10). Results were similar when we additionally adjusted for ambulatory blood pressure (Table S11), or for class of antihypertensive medication (Table S12). Furthermore, no statistically significant interaction was found for T2D status in our main analysis (P value for interaction 0.94), and analysis stratified by T2D status showed that results were qualitatively similar in individuals with and without T2D (Table S13).

Discussion

The present cross-sectional study found that MVD is associated with worse cognitive performance. This association was present for various MVD measures, including CSVD features, plasma biomarkers of MVD and UAE, but not retinal arteriolar and venular dilation responses or skin hyperemia. Furthermore, this association was independent of age, education level, sex, lifestyle factors, cardiovascular risk factors, current depression, and low-grade inflammation. The strength of the association of each SD higher MVD score on the cognitive function score was equivalent to the effect of one to 3 years of aging.

Our study agrees with previous studies that showed an association between individual MVD measures, that is, CSVD features,^{15,41} plasma biomarkers of MVD^{11–14} and UAE,¹⁶ and worse cognitive performance. Some of these studies, but not all, found an association between MVD and worse cognitive performance or cognitive impairment. Our study expands this knowledge, as it is the first to comprehensively evaluate the association between MVD measures in various vascular beds and cognitive performance in a large population-based study with extensive adjustment for confounders.

The results were consistent across various MVD measures, except for retinal arteriolar and venular dilation responses and skin hyperemia, which were not statistically

Table. Characteristics of the Study Population

Baseline Characteristics	Total Study Population (n=3011)	Tertiles of Cognitive Function Score		
		Lowest (n=1003)	Middle (n=1004)	Highest (n=1004)
Age, y	59.5 (8.2)	64.0 (6.8)	59.9 (7.3)	54.7 (7.8)
Women, %	48.9 (1471)	36.5 (366)	45.4 (456)	64.6 (649)
Education level, %				
Low	15.7 (472)	31.6 (317)	11.8 (118)	3.7 (37)
Intermediate	43.2 (1301)	44.8 (449)	45.1 (453)	39.7 (399)
High	41.1 (1238)	23.6 (237)	43.1 (433)	56.6 (568)
Smoking status, %				
Never	34.9 (1051)	31.8 (319)	33.9 (340)	39.0 (392)
Former	51.9 (1564)	52.8 (530)	53.8 (540)	49.2 (494)
Current	13.2 (396)	15.4 (154)	12.4 (124)	11.8 (118)
Alcohol use, %				
None	18.0 (543)	21.7 (218)	16.0 (161)	16.3 (164)
Low	55.5 (1671)	54.1 (543)	58.6 (588)	53.8 (540)
High	26.5 (797)	24.1 (242)	25.4 (255)	29.9 (300)
Body mass index, kg/m ²	27.1 (4.5)	28.0 (4.5)	27.0 (4.6)	26.2 (4.2)
Type 2 diabetes mellitus, %	26.5 (797)	41.2 (413)	25.0 (251)	13.2 (133)
Hypertension, %	55.4 (1667)	71.9 (721)	54.9 (551)	39.3 (395)
Total/HDL cholesterol ratio	3.7 (1.2)	3.7 (1.2)	3.8 (1.2)	3.6 (1.2)
Triglycerides, mmol/L	1.4 (0.9)	1.5 (0.9)	1.4 (0.8)	1.3 (0.8)
Lipid-modifying medication, %	34.9 (1050)	50.3 (505)	33.9 (340)	20.4 (205)
Prior cardiovascular disease, %	16.1 (486)	24.6 (247)	13.9 (140)	9.9 (99)
Current depression, %	3.7 (112)	5.4 (54)	3.6 (36)	2.2 (22)
Plasma biomarkers of low-grade inflammation composite score, SD*	0.0 (1.0)	0.2 (1.0)	0.0 (1.0)	-0.3 (1.0)
Microvascular dysfunction measures†				
Microvascular dysfunction composite score, SD	0.0 (1.0)	0.4 (1.1)	0.0 (0.9)	-0.4 (0.8)
Cerebral small vessel disease features				
Total brain parenchyma volume, mL	1138.4 (111.7)	1123.9 (111.8)	1150.3 (117.3)	1138.8 (104.6)
White matter hyperintensity volume, mL	0.2 (0.1–0.7)	0.4 (0.1–1.3)	0.2 (0.1–0.8)	0.1 (<0.1–0.4)
Presence of cerebral microbleeds	11.8 (237)	9.2 (92)	10.5 (73)	9.9 (72)
Presence of lacunar infarcts	5.4 (110)	6.7 (40)	6.4 (45)	3.4 (25)
Plasma biomarkers of microvascular dysfunction				
Soluble ICAM-1, µg/L	352.7 (98.1)	372.3 (116.4)	348.1 (86.7)	337.8 (84.7)
Soluble VCAM-1, µg/L	425.1 (99.8)	445.2 (111.4)	422.9 (97.9)	407.1 (84.6)
Soluble E-selectin, µg/L	117.5 (64.2)	130.1 (76.4)	117.6 (56.3)	104.9 (55.4)
Von Willebrand Factor (%)	131.7 (47.8)	140.9 (51.1)	130.8 (45.9)	123.5 (44.7)
Urinary albumin excretion				
Urinary albumin excretion ≥30 mg/24 h	8.1 (242)	13.4 (133)	7.0 (70)	3.9 (39)
Urinary albumin excretion 15–<30 mg/24 h	10.3 (308)	13.1 (130)	9.3 (93)	8.5 (85)
Flicker light-induced arteriolar and venular dilation response				
Flicker light-induced arteriolar dilation response (%)	3.1 (2.8)	2.7 (2.9)	3.1 (2.7)	3.3 (2.7)
Flicker light-induced venular dilation response (%)	3.9 (2.2)	3.7 (2.2)	3.9 (2.1)	4.0 (2.2)
Heat-induced skin hyperemia (%)	1133.2 (781.5)	1006.2 (760.5)	1208.6 (859.6)	1192.0 (701.6)

Data are presented as percentage of participants (n), mean±SD (SD) or median (interquartile range). HDL indicates high-density lipoprotein; ICAM-1, intercellular adhesion molecule-1; and VCAM-1, vascular adhesion molecule-1.

*Expressed per SD.

†Data available for microvascular dysfunction composite score n=2034; total brain parenchyma volume and white matter hyperintensity volume n=2049; lacunar infarcts n=2046; cerebral microbleeds n=2012; sICAM-1; sVCAM-1; and sE-selectin n=3011; vWF n=2991; urinary albumin excretion n=2987; retinal arteriolar dilation response n=2018; retinal venular dilation response n=2049; and skin hyperemia n=1457.

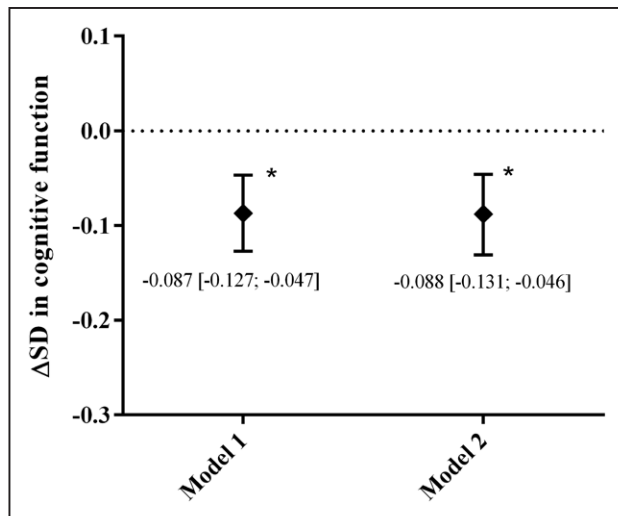


Figure 2. Association between microvascular dysfunction score and cognitive function score. *Statistical significance ($P < 0.05$). Data are available in $n = 2034$. Results are expressed as SD (95% CI) worse cognitive function score per SD higher microvascular dysfunction score. Results were adjusted for age, education level, sex, diabetes mellitus type 2, body mass index, smoking status, alcohol use, hypertension, total/HDL (high-density lipoprotein) cholesterol ratio, triglycerides, and lipid-modifying medication use (model 1), and additionally for prior cardiovascular disease, current depression and plasma biomarkers of low-grade inflammation (model 2).

significantly associated with cognitive performance. Retinal arteriolar and venular dilation response and skin hyperemia may mostly reflect a more subtle form of endothelium-dependent MVD, which may change acutely and may be reversible.²⁷ For example, microvascular dilation responses in the retina or skin are transiently decreased directly after smoking⁴² and consumption of caffeine.⁴³ In contrast, CSVD features, plasma biomarkers of MVD and UAE (all indirect measures of MVD) may reflect a more advanced stage of MVD.¹⁰ However, this study is the first to evaluate the association between retinal arteriolar and venular dilation response and skin hyperemia and cognitive function, and this issue, therefore, requires further study.

In the present study, the association between MVD and worse cognitive performance was stronger in participants aged ≥ 65 years versus < 65 years. This corresponds to our previous study on UAE and cognitive performance,²² and may be explained by a higher susceptibility for the detrimental effects of MVD on cognitive performance in the presence of a lower

cognitive reserve with increasing age, in accordance with the cognitive reserve hypothesis.³⁵

The observation that various MVD measures were associated with worse cognitive performance in our study supports the hypothesis that MVD may play a role in the pathophysiology of cognitive impairment. Earlier studies showed that impaired neurovascular coupling, cerebral autoregulation,² blood-brain barrier leakage,⁴⁴ and impaired neurogenesis⁴⁵ are present in individuals with mild cognitive impairment and Alzheimer's disease, and these disturbances may be the consequence of MVD.²

Other underlying mechanisms may, however, explain the observed associations. First, MVD often coexists with CVD, and CVD is associated with worse cognitive performance.⁴⁶ However, our results were independent of a large set of cardiovascular risk factors and prior CVD. Second, depression and low-grade inflammation are related to both MVD and worse cognitive performance. Our results remained, however, after adjustment for these factors. Third, other biological mechanisms may underlie both MVD and worse cognitive performance. For example, oxidative stress and lower brain-derived neurotrophic factor have been associated with both MVD and worse cognitive performance.^{47–50} However, data on oxidative stress and brain-derived neurotrophic factor were unavailable in our study; this requires further study.

Our study has several limitations. First, the cross-sectional observational design precludes reaching causal conclusions about the study findings. Second, the construction of the composite scores assumes that all its components reflect cerebral MVD, which is not necessarily true. Our a-priori defined composite score was calculated with use of indirect and direct measures, which may reflect different forms of MVD (acute and reversible versus more advanced), and this may have led to an underestimation of the association between (a more advanced stage of) MVD and worse cognitive function. Third, no data were available on Alzheimer's disease pathologies, such as amyloid and tau deposition. It has been hypothesized that these pathologies and MVD may act synergistically (ie, interact) in the development of cognitive impairment.⁵¹ Such interaction might explain our observed association between MVD and worse memory, a domain most strongly associated with Alzheimer's disease, and this issue requires further study. Fourth, lower total brain parenchyma volume is also determined by factors other than microvascular disease, particularly the process of neurodegeneration. Fifth,

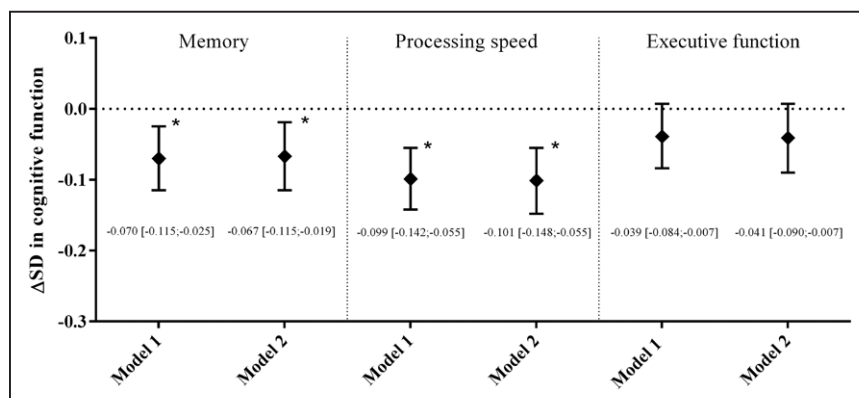


Figure 3. Associations between microvascular dysfunction score and domain-specific cognitive function score. *Statistical significance ($P < 0.05$). Data are available in $n = 2034$. Results are expressed as SD (95% CI) worse domain-specific cognitive function score per SD higher microvascular dysfunction score. Adjustments as in Figure 2.

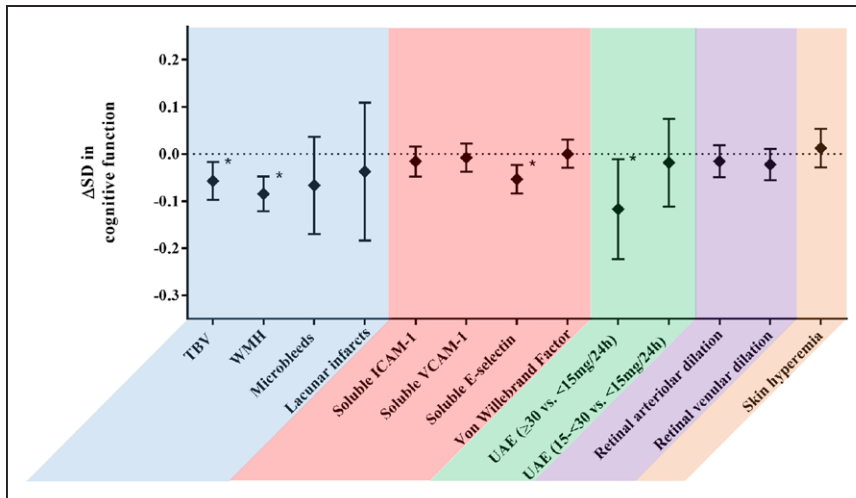


Figure 4. Associations between individual measures of microvascular dysfunction and cognitive function score. *Statistical significance ($P < 0.05$). Results are expressed as (SD (95% CI) worse cognitive function score per SD lower total brain parenchyma volume and higher white matter hyperintensity volume, presence of lacunar infarcts and microbleeds, per SD higher plasma biomarkers of microvascular dysfunction, urinary albumin excretion ≥ 30 vs < 15 mg/24 h, urinary albumin excretion between 15 and < 30 vs < 15 mg/24 h, per SD lower retinal arteriolar and venular dilation response, and per SD lower skin hyperemia. Adjustments as in Figure 2, model 2. ICAM-1 indicates intercellular adhesion molecule-1; TBV, total brain parenchyma volume; UAE, urinary albumin excretion; VCAM-1, vascular adhesion molecule-1; and WMH, white matter hyperintensity volume.

the study population consisted of middle and early-old aged participants without dementia who were relatively well-educated and whose cardiovascular risk factors were relatively well-controlled. This may have led to an underestimation of the reported findings due to lower variation in cognitive performance and relatively high cognitive reserve.

In conclusion, the present study shows that MVD is associated with worse cognitive performance.

Perspectives

This study supports the hypothesis that MVD contributes to the development cognitive impairment. MVD might, therefore, be a target for prevention strategies of cognitive impairment. Evidence suggests that lifestyle modifications, such as weight loss and exercise, may, at least in part, favorably influence MVD.⁵² In addition, drugs, such as renin-angiotensin-aldosterone system inhibitors and antihyperglycemic agents (ie, metformin and GLP-1R (glucagon-like peptide 1 receptor) agonists), may improve microvascular function,⁵² possibly beyond their blood pressure- or glucose-lowering effects.⁵² Future longitudinal studies are needed to further evaluate the association of MVD and cognitive decline and dementia.

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Novelty and Significance

What Is New?

- We tested for the first time the association between various microvascular dysfunction measures and cognitive performance in a large population-based study.
- Microvascular dysfunction was measured by magnetic resonance imaging features of cerebral small vessel disease, plasma biomarkers of microvascular dysfunction, albuminuria, flicker light-induced retinal arteriolar and venular dilation and skin hyperemia.

What Is Relevant?

- We found an association between a composite score of microvascular dysfunction and worse cognitive performance.

- Retinal arteriolar and venular dilation response and skin hyperemia were not associated with cognitive performance.

Summary

- Our findings support the hypothesis that microvascular dysfunction contributes to cognitive impairment.
- Microvascular dysfunction may be a target for prevention strategies of cognitive impairment.
- Future longitudinal studies are needed to further evaluate the association of microvascular dysfunction and cognitive decline and dementia.